Global burden of acute lower respiratory infection associated with human metapneumovirus in children under five years for 2018

Global burden of acute lower respiratory infection associated with human metapneumovirus in children under five years for 2018: a systematic review and modelling study

Xin Wang PhD[1], You Li PhD[1], Maria Deloria-Knoll PhD[2], Prof. Shabir A Madhi PhD[3], Cheryl Cohen MD[4], Asad Ali MD*[5], Prof. Sudha Basnet MD*[6], Prof. Quique Bassat MD*[7], W. Abdullah Brooks MD*[2], Malinee Chittaganpitch MSc*[8], Marcela Echavarria PhD*[9], Rodrigo A Fasce BSc*[10], Doli Goswami MSc*[11], Siddhivinayak Hirve PhD*[12], Nusrat Homaira PhD*[11,13], Stephen R.C. Howie PhD*[14], Prof. Karen L. Kotloff MD*[15], Prof. Najwa Khuri-Bulos MD*[16], Prof. Anand Krishnan MD*[17], Marilla G Lucero MD*[18], Socorro Lupisan MD*[18], Ainara Mira-Iglesias MSc*[19], David P. Moore PhD*[20], Cinta Moraleda PhD*[21], Marta Nunes PhD*[3], Prof. Histoshi Oshitani MD*[22], Betty E Owor PhD*[23], Prof. Fernando P Polack MD*[24], Prof. Katherine L. O'Brien MD*[2], Zeba A Rasmussen MD*[25], Prof. Barbara A Rath MD*[26], Vahid Salimi PhD*[27], Prof. J. Anthony G. Scott FRCP*[28], Prof. Eric AF Simões MD*[9], Prof. Tor A Strand PhD*[30], Prof. Donald M. Thea MD*[31], Florette K Treurnicht PhD*[4], Linda C Vaccari MbChB*[1], Prof. Lay-Myint Yoshida PhD*[32], Prof. Heather J Zar PhD*[33], Prof. Harry Campbell MD[1], Prof. Harish Nair PhD[1], for the Respiratory Virus Global Epidemiology Network

* Authors listed alphabetically

Correspondence to: Prof Harish Nair, PhD, Centre for Global Health, Usher Institute, Edinburgh Medical School, University of Edinburgh, Teviot Place, Edinburgh EH8 9AG, UK. harish.nair@ed.ac.uk

1 Centre for Global Health, Usher Institute, Edinburgh Medical School, University of Edinburgh, Edinburgh, Scotland, UK.

2. Department of International Health, International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA.

3. Medical Research Council: Respiratory and Meningeal Pathogens Research Unit; Department of Science and Technology/National Research Foundation: Vaccine Preventable Diseases, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.

4. Centre for Respiratory Disease and Meningitis, National Institute for Communicable Diseases, Johannesburg, South Africa and School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.

5. Department of Pediatrics and Child Health, Aga Khan University, Karachi, Pakistan.

6. Department of Child Health, Tribhuvan University, Kathmandu, Nepal; the Centre for International Health, University of Bergen, Norway.

7. Barcelona Global Health Institute, Hospital Clínic–University of Barcelona, Barcelona, Spain; Centro de Investigação em Saúde de Manhiça, Maputo, Mozambique; Institució Catalana de Recerca i Estudis Avançats, Barcelona, Spain; Pediatric Infectious Diseases Unit, Pediatrics Department, Hospital Sant Joan de Déu (University of Barcelona), Barcelona, Spain; Consorcio de Investigación Biomédica en Red de Epidemiología y Salud Pública, Madrid, Spain.

8. Medical Sciences Technical Office, Department of Medical Sciences, MoPH, Thailand.

9. Clinical Virology Unit, Centro de Educación Médica e Investigaciones Clínicas, Argentina.

10. Public Health Institute of Chile, Región Metropolitana, Chile.

11. International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), Dhaka, Bangladesh.

12. KEM Hospital Research Centre, Pune, Maharashtra, India.

13. Discipline of Paediatrics, School of Women's and Children's Health, The University of New South Wales (UNSW), Sydney, Australia.

14. Medical Research Council Unit, The Gambia at London School of Hygiene & Tropical Medicine; Department of Paediatrics, University of Auckland, New Zealand

15. Department of Pediatrics and Department of Medicine, Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore, MD, USA

16. Department of Pediatrics, University of Jordan school of medicine, Amman, Jordan.

17. Centre for Community Medicine, All India Institute of Medical Sciences, New Delhi, India.

18. Research Institute for Tropical Medicine, Muntinlupa, Philippines.

19. Área de Investigación en Vacunas, Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (Salud Pública), Valencia, Spain.

20. Medical Research Council: Respiratory and Meningeal Pathogens Research Unit University of the Witwatersrand, Johannesburg, South Africa; Department of Paediatrics & Child Health, Chris Hani Baragwanath Academic Hospital and University of the Witwatersrand, South Africa.

21. Barcelona Global Health Institute, Hospital Clínic–University of Barcelona, Barcelona, Spain; Infectious Pediatric Diseases Section, Hospital Universitario de Octubre, Universidad Complutense, Research Institute Hospital de Octubre, Madrid, Spain.

22. Department of Virology, Tohoku University Graduate School of Medicine, Miyagi, Japan.

23. KEMRI–Wellcome Trust Research Programme, Kilifi, Kenya.

24. Fundacion INFANT, Buenos Aires, Argentina.

25. Fogarty International Center, National Institutes of Health, Bethesda, MD, USA

26. Vienna Vaccine Safety Initiative, Berlin, Germany.

27. Department of Virology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.

28. KEMRI-Wellcome Trust Research Programme, Centre for Geographic Medicine Research - Coast, Kilifi, Kenya; Nuffield Department of Tropical Medicine, Oxford University, Oxford, UK; Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK.

29. Department of Pediatrics, Section of Infectious Diseases, University of Colorado, School of Medicine; Department of Epidemiology and Center for Global Health, Colorado School of Public Health, Aurora CO, USA.

30. Innland Hosptial Trust, Lillehammer, Norway and the Centre for International Health, University of Bergen, Norway.

31. Department of Global Health and Development, Boston University School of Public Health, Boston, MA, USA.

32. Department of Pediatric Infectious Diseases, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan.

33. Department of Paediatrics & Child Health and Medical Research Council unit on Child & Adolescent Health, University of Cape Town, Cape Town, South Africa.

Summary

Human metapneumovirus (hMPV) is one of several important viruses associated with childhood acute lower respiratory infection (ALRI). However, there are currently no global burden estimates for ALRI associated with hMPV in children, and there are no licenced vaccines or drugs for hMPV infections. We estimated age–stratified global morbidity and mortality burden of hMPV–associated ALRI among children under five years using data on laboratory–confirmed hMPV burden from different geographic regions.

Methods

We performed a systematic review of hMPV burden studies published between 1 January 2001 and 31 December 2019 and identified a further 40 high–quality unpublished studies. We assessed the risk of bias using a modified Newcastle–Ottawa Scale. Incidence rates, hospital admission rates, and in–hospital case–fatality ratios (hCFRs) of hMPV–associated ALRI (defined as ALRI with laboratory–confirmed hMPV) were analysed using a generalized linear mixed model. We applied incidence and hospital admission rates of hMPV–associated ALRI to population estimates to yield the morbidity burden estimates. We estimated hMPV–associated ALRI in–hospital deaths by combining hospital admissions and hCFRs of hMPV–associated ALRI. We estimated the overall hMPV–associated ALRI deaths (both in–hospital and out–hospital deaths) using the number of in–hospital deaths, population–based childhood pneumonia mortality, and care–seeking for child pneumonia. We also estimated hMPV–attributable ALRI cases, hospital admissions, and deaths (ALRI burden that are causally attributable to hMPV) by combining hMPV–associated burden estimates and attributable fractions of hMPV in laboratory–confirmed hMPV cases and deaths.

Findings

We estimated in 2018 that hMPV could be detected in 14.2 million (UR 10.2–20.1) ALRI cases, 643,000 (UR 425,000–977,000) hospital admissions, 7,700 (UR 2,600–48,800) in–hospital deaths, and 16,100 (UR 5,700–88,000) overall ALRI deaths among children under five years globally. Of these cases and deaths, an estimated 11.1 million (UR 8.0–15.7) ALRI cases, 502,000 (UR 332,000–762,000) ALRI hospital admissions, and 11,300 (UR 4,000–61,600) ALRI deaths could be causally attributable to hMPV. hMPV–associated ALRI incidence rate in the community setting did not vary much by age strata, while about 58% of hospital admissions were in infants less than 12 months; 64% of in–hospital deaths occurred

in the first six months of life, of which 80% occurred in low– and lower–middle income countries.

Interpretation

Infants younger than one year have disproportionately high risks of severe hMPV infections across settings, similar to respiratory syncytial virus and influenza virus. Infants younger than 6 months in low– and lower–middle income countries are at greater risk of death from hMPV–associated ALRI compared with other countries. Our mortality estimates, though likely to be conservative and underestimate the true hMPV mortality burden, demonstrate the importance of intervention strategies for infants across all settings, and warrant continued efforts to improve the outcome of hMPV–associated ALRI among young infants in low– and lower–middle income countries.

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Research in context

Evidence before this study

Human metapneumovirus (hMPV) is a common virus in children with ALRI. Two recent pooled analyses among different populations have shown that hMPV are identified in 6.1–6.4% of ALRI among patients under 20 years of age. However, no global estimates of hMPV–associated ALRI burden in children under 5 years have been made. One of the challenges to estimating global hMPV burden is the paucity of data on incidence of hMPV infections in published population–based studies that demonstrate the impact of the virus in defined populations.

Added value of this study

Our analysis was based on data on laboratory–confirmed hMPV ALRI (hMPV–associated ALRI) morbidity and mortality burden. We incorporated 159 studies with data on hMPV–associated ALRI community incidence rates, hospital admission rates, hospitalised proportion positives, and in–hospital case–fatality ratios, including 40 high quality unpublished studies that provided data stratified by narrow age groups in children under 5 years. 27% of the data were from low–income and lower middle–income countries. Our hMPV–associated ALRI burden estimates by different settings and narrow age groups revealed the subgroup populations most vulnerable to hMPV–associated ALRI morbidity and mortality, providing evidence regarding the target populations and settings for future intervention studies and informing intervention strategies. Since the presence of hMPV in the upper respiratory tract in children with ALRI does not indicate causation, we reported global burden of ALRI that are causally attributable to hMPV (hMPV–attributable ALRI burden), which could help understand the role of this virus in causing childhood ALRI. We estimated that hMPV could be identified in 11% of ALRI cases, 4–13% of ALRI hospital admissions, and 2% of ALRI deaths among children under 5 years globally. After accounting for the causal attribution of hMPV, we estimated that 8% of ALRI cases, 3–10% of ALRI hospital admissions, and 1% of ALRI mortality could be attributed to hMPV. About 58% of these hospital admissions occurred in the first year of life. About 64% of the in–hospital deaths occurred in infants younger than 6 months, including 80% occurring in low– and lower middle–income countries.

Implications of all the available evidence

Our systematic review provides the first estimates of global hMPV–associated ALRI and hMPV–attributable ALRI morbidity and mortality in children under 5 years, by narrow age bands. Our results indicate that infants less than 1 year of age have increased risk of severe hMPV–associated ALRI compared with older children. Infants younger than 6 months, especially those in low– and lower middle–income countries, are at greater risk of death from hMPV–associated ALRI compared with other countries. These findings warrant continued efforts to develop targeted intervention strategies to protect infants from hMPV infections, and to improve the outcome of infants with hMPV–associated ALRI, especially in low– and lower–middle income countries. Such strategies could include, for example, specific antiviral therapeutics, monoclonal antibodies, or vaccination for children and/or their mothers during pregnancy.

Introduction

Acute lower respiratory infections (ALRI) are one of the leading causes of morbidity and mortality in children globally, accounting for 10% of mortality in children under five years in 2017.[1] Human metapneumovirus (hMPV), first identified in 2001, is an important virus causing ALRI in young children.[2-5] Previous evidence indicates that almost all children have been infected with hMPV by the age of five, and with most severe infections occurring in infants.[6-10]. Available pooled analyses among different populations have focused on broad age groups, and have shown that hMPV is associated with 6.1–6.4% of hospitalised ALRI among patients under 20 years of age worldwide.[11,12] Incidence and mortality of hMPV–associated ALRI have only been available in a very limited number of published literature, especially for narrow age groups. There are no global or regional burden estimates for children under five years.

Using the published and unpublished data on laboratory–confirmed (culture, immunofluorescence assay, or molecular test) hMPV morbidity and mortality, we sought to estimate the global and regional number of hMPV–associated ALRI cases, hospital admissions, and mortality by age strata in children under five years for 2018. Since the presence of hMPV in children's upper respiratory tract does not imply causation, we estimated the global burden of ALRI that are attributable to hMPV by accounting for the causal attribution of hMPV.

The estimates would provide evidence for the further development of targeted interventions and treatment. A live–attenuated recombinant hMPV vaccine has been evaluated in a recent phase I clinical trial, though the result showed that the vaccine was over–attenuated for children aged 6–59 months.[13] Antivirals against hMPV infections and several other types of vaccines have been investigated, but have not reached clinical trials.[14-16]

Methods

Systematic review, definitions, and assessment of risk of bias

We conducted a systematic review on hMPV–associated ALRI burden in children under five years (appendix pp 4–5). We searched Medline (Ovid), Embase (Ovid), Global Health (Ovid: 1973 onwards), CINAHL, Web of Science, Global Health Library, three Chinese databases (CNKI, Wanfang and Chongqing VIP), and Google (for grey literature). No language or publication restrictions were applied, and three reviewers (XW, LCV and YL) screened the titles and abstracts for eligibility and extracted data independently. Disagreements were

resolved by discussion between the reviewers. We supplemented the data from published studies with additional high-quality unpublished data (from ongoing studies or re–analysis of previously published studies) using agreed standardised approaches and definitions within a collaborative network - the Respiratory Virus Global Epidemiology Network.[17]

We included studies that were published between January 1, 2001, and December 31, 2019, and reported any of the following data for children under five years: community incidence rates of ALRI (i.e., clinical pneumonia according to 2005 WHO Integrated Management of Childhood Illnesses[18]) with laboratory–confirmed hMPV; hospital admission rates of ALRI (i.e., physician–confirmed diagnosis of ALRI) or ALRI with hypoxaemia with laboratory–confirmed hMPV; proportions of hospitalised ALRI with laboratory–confirmed hMPV; in–hospital case–fatality ratios (hCFRs) of ALRI with laboratory–confirmed hMPV. Details of case definitions are in appendix pp 2–3.[19]

Studies had to use a clear case definition for specimen collection and testing, and studies that reported incidence and hospital admission rate data had to show data for at least one complete calendar year (or at least one full influenza season if in a temperate region). We included hCFR data for any length of study period. We included proportion positive data if they were for at least one full calendar year. We excluded studies: without a clear denominator population at risk (limited to those reporting incidence and hospital admission rate data); those in which hMPV was not the primary outcome; reporting modelled burden estimates; those in which hMPV infections were diagnosed based on serology alone; only including population subgroups with high–risk conditions.

We used a modified Newcastle–Ottawa Scale to assess the risk of bias in seven domains, including study design, adjustment for health utilization, patient groups excluded, definition, sampling strategy, diagnostic testing, and hypoxaemia ascertainment (appendix pp 25–26).[19,20]

Statistical analysis

Our approach to burden estimation, including main analyses and sensitivity analyses is summarised in appendix p14. We estimated hMPV–associated ALRI cases, hospital admissions, and in–hospital deaths using a strategy similar to our previous analysis.[19] First, we estimated incidence rates, hospital admission rates, and hCFRs of hMPV–associated ALRI using a generalized linear mixed model.[21] For the incidence rate and hospital admission

rate, we scaled the population–at–risk for the level of testing per study where available before meta-analyses (appendix p 23).

hMPV-associated ALRI morbidity burden estimation

After meta-analyses, we chose Monte Carlo Simulation to estimate morbidity burden as it allows us to combine meta-estimates and population estimates (United Nations population estimates for 2018).[22] The median value of 10,000 samples simulated from a log–normal distribution was used as the point burden estimate and the 2·5th and 97·5th percentiles as the 95% uncertainty ranges (UR). We followed the same strategy to promote consistency with our previous studies; other methods (e.g., resampling observed data) may yield comparable estimates.[23] In the main analysis, we reported estimates stratified by three non–overlapping age bands (0–5 months, 6–11 months, and 12–59 months) and by 2018 child mortality settings (low; high: using the median value of under–five mortality rate, 16.6 per 1,000 live births, as the cut–off point) for each outcome where available.[24] Global results are calculated as the sum of age– and region–specific estimates. The numbers of cases and deaths were rounded to the nearest thousand and hundred, respectively. In the community setting, we reported the incidence rate for the overall age band (0–59 months) as data were insufficient to allow disaggregation by narrower age bands. To incorporate information from studies with data for other age bands (e.g., 0-11 months), we imputed the numbers of cases for 0-59 months using a multiple imputation approach as was done previously (appendix pp 21–22).[19]

hMPV–associated ALRI in-hospital deaths

We estimated hMPV–associated ALRI in–hospital deaths by combining the estimates of hospital admissions and hCFRs of hMPV–associated ALRI.[17,25] Similar to morbidity estimation, global estimates of mortality are calculated as the sum of the estimates by the three age groups and by child mortality settings.

Overall hMPV–associated deaths

Many child ALRI deaths occur outside hospitals, especially in resource-limited settings due to the poor care-seeking and / limited access to care. We estimated a ratio (“inflation factor”) of overall ALRI deaths to in–hospital ALRI deaths at eight sites in six high child mortality countries (Mozambique, Kenya, South Africa, Burkina Faso, and Ghana in sub–Saharan Africa, Bangladesh in South Asia),[19,26-28] We calculated the median inflation factor which was extrapolated to other high child mortality countries, and combined with estimates of in–hospital deaths to yield overall hMPV–associated ALRI mortality (appendix p15).[17,25,29] We

assumed that hMPV prevalence was the same in ALRI deaths in community and in hospitals. For low child mortality settings, the reciprocal of the proportion of children with pneumonia symptoms who received care, measured in Multiple Indicator Cluster Surveys, Demographic and Health Surveys and other national surveys, was used as a proxy for inflation factor.[30] This measure is available in many countries and regions, and can thus help improve the generalisation. The median inflation factor was extrapolated to other low child mortality countries without data. Compared to approximating the inflation factor using non-specific ALRI mortality, in this approach we assumed that the case-fatality ratios for pneumonia in hospitalised and non-hospitalised cases were broadly similar.

hMPV-attributable cases, hospital admissions, and deaths

The presence of hMPV in the upper respiratory tract of a child with ALRI may not indicate a causal association between hMPV and ALRI. Thus, we estimated the ALRI burden causally attributable to hMPV (i.e., hMPV–attributable ALRI burden) by combining (1) the hMPV–associated ALRI burden estimates and (2) the fraction of laboratory–confirmed hMPV ALRI cases or deaths that are attributable to hMPV – or, the attributable fraction of hMPV in hMPV–associated ALRI cases or deaths. For the attributable fraction for hMPV–associated ALRI cases, we used a median value of 78% as the input based on three multi–country studies.[3-5] The attributable fraction of hMPV–associated ALRI deaths was calculated using the attributable fraction of hMPV–associated ALRI cases and the ratio between hCFRs of hMPV–positive ALRI and hMPV–negative ALRI. We assumed that hCFR of hMPV negative ALRI was equal to that for those tested positive but not attributable to hMPV (detailed formulas in appendix p17).

Sensitivity analyses

In sensitivity analyses for hMPV–associated ALRI morbidity and in–hospital deaths, we reported estimates by country development status according to UNICEF definitions and by World Bank income levels (low– and lower–middle income, upper–middle income, and high–income).[32,33] We additionally estimated the range of hMPV–associated ALRI hospital admissions by combining the proportion positives of hMPV in ALRI hospital admissions and the recent estimates of all-cause ALRI hospital admissions among children under five years.[34,35]We estimated overall hMPV–associated ALRI deaths for high child mortality settings in a sensitivity analysis by applying the proportion positives of hMPV in ALRI deaths to the number of ALRI deaths in children under five years for 2017.[1] The proportion

of hMPV positives in ALRI deaths was estimated using data from hospital-based studies in the systematic review.

We estimated hMPV–attributable mortality for high child mortality settings in a sensitivity analysis by applying the proportion of hMPV–attributable ALRI deaths to the number of ALRI deaths in children under five years for 2017. The proportion of hMPV–attributable ALRI deaths was estimated using data for the period December 2016 to October 2019 from Child Health and Mortality Prevention Surveillance.[36,37] Details are in appendix p18. We reported the estimates from the main analysis. Sensitivity results are available in the appendix (pp 8–13, 16, 19). Details of included studies are available in the appendix (pp 34– 53). All analyses were done in R version 3.5.2.[38,39] This study was conducted and reported in accordance with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) recommendations (appendix pp 59).[40]

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. XW and HN had full access to all the data in the study and HN had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the study selection for the systematic review. Overall, we identified 159 studies with data on hMPV–associated ALRI community incidence (10 studies), hospital admission rates (39 studies), hospitalised proportion positives (116 studies), and hCFRs (73 studies). Of these studies, 40 were unpublished studies from the collaboration network and 119 studies from published literature. By World Bank income level, 7 studies were from low–income countries, 36 from lower–middle income countries, 67 from upper–middle income countries, and 49 from high–income countries. The number of studies by characteristics for each outcome are summarised in appendix (pp6–7).

We identified 11 studies reporting the incidence of hMPV–associated ALRI. There were ten studies with data for 0–59 months after imputation, including six studies from high child mortality settings; five studies from lower–middle income countries, two studies from upper–middle income countries, and three studies from high–income countries. Four studies reported the rates for the pre–2010 period. The hMPV–associated ALRI incidence rate meta–estimate was 22.1 (95%CI 17.0–28.7) per 1,000 children per year for 0–59 months in high child mortality settings, and 18.9 (95%CI 11.2–31.9) for low child mortality settings. Thus,

we estimated 14.2 million (UR 10.2–20.1) hMPV–associated ALRI cases globally in children under five years (Table 1).

We identified 39 studies reporting hMPV–associated ALRI hospital admission rates, including 29 studies reporting data by three narrow age bands (0–5 months, 6–11 months, or 12–59 months). The hospital admission rate meta–estimate was more than 4–fold higher in infants aged 0–5 months and 6–11 months (2.2–3.3 per 1,000 children per year) than for children aged 12–59 months (0.3–0.6 per 1,000 children per year) across World Bank income levels and child mortality settings (Table 2). In the analysis stratified by child mortality settings, we estimated 643,000 (UR 425,000–977,000) hMPV–associated ALRI hospital admissions globally in children under five years.

There were 14 studies reporting hospital admission rates for hMPV–associated ALRI with hypoxaemia by three age groups, including five studies were from low child mortality settings. In the analysis stratified by child mortality settings, we estimated 112,000 (UR 29,000–522,000) hospital admissions for hMPV–associated ALRI with hypoxaemia in children aged 0–59 months globally, accounting for 17% (112,000/643,000) of the hMPV–associated ALRI hospital admissions (Table 2).

A total of 73 studies reported hCFRs for hMPV–associated ALRI in children under five years, including 28 studies with data stratified by three narrow age bands. Infants aged 0–5 months from high child mortality settings and lower–middle income countries had highest hCFRs [4.5% (95%CI 2.3–8.6) for lower–middle income countries; 3.3% (95%CI 1.7–6.1) for the high child mortality setting]. The hCFRs were lower for children aged 6–11 months and 12–59 months and for high–income countries (0.5–1.1%), with wide confidence intervals (Table 3). Based on these meta–estimates, we estimated 7,700 (UR 2,600–48,800) hMPV–associated ALRI in–hospital deaths in children under five years. About 64% of these deaths were in young infants aged 0–5 months (4,900/7,700), and 88% (6,800/7,700) occurred in countries with high child mortality.

Across 28 countries or regions with low child mortality, 22% to 94% of children with pneumonia received care from a health provider. About 71% of the data were from the period between 2010 and 2014. Based on these data, we estimated the median inflation factor was 1·3 across regions or countries, and 1,100 (UR 100–28,800) overall hMPV–associated ALRI

deaths among children under five years for low child mortality settings. Of the eight sites with data on pneumonia mortality in high child mortality settings, five sites were from rural areas, and six from African countries. Six studies reported data from the period between 2010 and 2016, and the remaining two studies reported data from 2008 onward. The inflation factor ranged from 1·5 to 3·5 across the eight sites, with a median value of 2·2. Thus, we estimated 14,900 (UR 5,600–59,700) overall hMPV–associated ALRI deaths in high child mortality settings, and 16,100 (UR 5,700–88,000) deaths globally.

Applying attributable fraction of hMPV to the above estimates reporting hMPV-associated burden, we estimated that 11.1 million (UR 8.0–15.7) ALRI cases and 502,000 (UR 332,000–762,000) ALRI hospital admissions could be attributed to hMPV in children under five years (Table 4). We estimated that the ratio of case–fatality of hMPV–attributable ALRI to hMPV–associated cases was 0.9, and the AF for hMPV–associated ALRI deaths was 70% (appendix p17–18). This suggested that 11,300 (UR 4,000–61,600) overall ALRI deaths could be attributed to hMPV, including 10,400 (UR 3,900–41,800) in high child mortality settings (Table 4).

We conducted several sensitivity analyses to estimate hospital admissions, in–hospital deaths, and overall deaths of hMPV–associated ALRI, and deaths of hMPV–attributable ALRI. For global hMPV–associated ALRI hospital admissions, the estimates in children under five years ranged from 626,000 to 650,000 in analyses by different stratification groups (Appendix p9); the proportion–based approach yielded a broader range (e.g., from 282,000 to 902,000) (Appendix p10). The point estimate of global in–hospital deaths ranged from 7,200 to 9,100 in children under five years, and an estimated 78% of the global in–hospital deaths occurred in lower–middle income countries (7,200/9,100) based on the results by World Bank income level (appendix p11). We estimated 19,900 (UR 12,100–33,200) hMPV–associated ALRI deaths and 9,900 (UR 2,600–39,300) hMPV–attributable ALRI deaths in children aged 1–59 months in high child mortality settings in sensitivity analyses (appendix p16; 19).

Discussion

We reported the first global hMPV–associated ALRI burden estimates among children under 5 years, by narrow age bands. Our estimates suggest that hMPV are detected in 11% of ALRI cases, 4–13% of ALRI hospital admissions, and 2% of ALRI deaths among children under

five years globally.[1,34,35] About 8% of ALRI cases, 3–10% of ALRI hospital admissions, and 1% of ALRI mortality can be attributed to hMPV. The wide uncertainty ranges of the present burden estimates reflected differences across studies, arising from variation in hMPV epidemiology between populations and methodological differences, and paucity of data, especially mortality data.

We demonstrated that as has been shown for RSV and influenza, the hMPV–associated ALRI hospital admission rate was much higher in infants, with about 58% of hospital admissions and 71% in–hospital deaths in children under five years occurring in the first year of life.[17,19] This could be due to the immaturity of infant's immune system and decaying maternal antibodies over the first several months of life.[41,42] The consistently high hMPV–associated ALRI hospital admission rate among infants across different settings highlights the importance of developing safe and effective maternal hMPV vaccines and vaccines for infants.

Our hCFR estimates show that young infants aged 0–5 months are at an increased risk of hMPV–associated ALRI mortality. hCFR estimates for 0–5 months varied substantially across settings, possibly reflecting the differences in disease severity at admission and in the quality of hospital care. Increased disease severity at presentation could be related to the high prevalence of certain underlying conditions and delays in care–seeking.[3,35] The CFR (overall and in–hospital) and overall mortality due to ALRI among children under five years substantially reduced in the past 15 years due to socioeconomic development, reduced prevalence of pneumonia risk factors, and increased use of interventions.[35,43] However, there were very few hMPV–associated ALRI deaths (1–3 deaths) in multi–year studies, and we were unable to observe any trends in the hCFR of hMPV–associated ALRI. Using available age–stratified data prior to 2010 (eligible if part of a study was from pre–2010 when data could not be stratified by year), we estimated 9,600 (UR 2,300–51,200) hMPV–associated ALRI in–hospital deaths among children under five years for 2010 (appendix p12).

For high child mortality settings, the inflation factor was based on limited data.[17] Although the inflation factor was only applied to high child mortality countries, there may be bias due to limited generalisability and location specific characteristics (prevalence of hMPV in childhood ALRI deaths). Nevertheless, our reported estimates for high child mortality settings are conservative and could increase by approximately 30% (19,900) using an alternative estimation approach (appendix p16). For low child mortality settings, the inflation factor and overall mortality estimate is likely underestimated because the definition of "care–

seeking" is broader than the definition of "in–hospital": contact with primary care is included as "care–seeking" in surveys, but are not included in the "in–hospital mortality" estimates in the present analysis. The US vital statistics data show that about 40% of under–five ALRI deaths (ICD–10 J09–22; U04) occurred in outpatient or emergency departments during 2010–2017.[44] Additionally, this analysis was based on one further assumption that there is no difference in CFR for hospitalised and non-hospitalised pneumonia cases. The direction of bias related to this assumption could be complicated by the two–way association between disease severity and care–seeking: children with more severe symptoms are more likely to receive hospital care; on the other hand, supportive care in hospitals can reduce the risk of death, and lack of appropriate care or delays in care can lead to rapid deterioration.[45-47] Moreover, data on pneumonia care–seeking in high–income countries have not been available in published reports; extrapolation from other low child mortality countries to high–income countries might cause bias. The estimates of inflation factor could also be affected by accuracy of assessment and completeness of documentation for ALRI or pneumonia. For example, the diagnosis of (presumptive) pneumonia in the UNICEF dataset is based on caregivers' report, thus may be inaccurate and affect the estimates of inflation factor.

In addition to the above, several other limitations are noted. Very few data were identified in Europe and Latin America, which could have affected the generalisation of the estimates. Moreover, heterogeneity in the methodology (variations in precise case definitions, proportion of eligible ALRI cases tested for hMPV) existed across studies for each outcome and could have likely biased our estimates (appendix p7). We adjusted for levels of testing when estimating hospital admission rates by assuming that the proportion positivity for hMPV was the same in those tested and untested. However, we did not adjust for the under–detection when estimating hCFRs. The hCFR of hMPV–associated ALRI and in–hospital mortality might be underestimated, as suggested by the higher hCFR in those tested compared to those untested (appendix p24). The incidence and hospital admission rates of hMPV–associated ALRI are unlikely to be affected by the accuracy of test methods as 92% of the studies used polymerase chain reaction to detect hMPV. In addition to potential biases as described above, we summed yearly data to ensure precision in the age–stratified analysis, but while doing this we did not account for the variation across years (appendix p20).

Our results show that infants under one year old have disproportionately high risks of severe hMPV infections across settings. Infants aged 0–5 months in low– and lower middle–income countries are susceptible to increased risk of mortality from hMPV–associated ALRI

compared with other countries, accounting for nearly 8 of every 10 global deaths occurring in this age group. These estimates highlight the importance of interventions for infants. For low– and lower middle–income countries, continued efforts are needed to reduce hMPV–associated ALRI mortality among young children, especially infants, in hospitals and communities through improving access to care and case management in hospitals. In light of the paucity of data at regional levels, these estimates should be viewed as preliminary estimates. In future, additional high–quality data on childhood hMPV–associated ALRI cases, hospital admissions, and mortality, especially age–stratified data, would help refine the estimates and track the trends of hMPV–associated ALRI morbidity and mortality.

Contributors

HN and HC conceptualised the study. XW led the literature review. LCV and YL independently screened literature and extracted data. XW led the data analysis with contributions from YL and MDK. XW, HN, HC, MDK, SAM, and CC led the data interpretation. XW wrote the first draft of the manuscript with input from HN, HC, MDK, SAM, and CC. All named authors of the Respiratory Virus Global Epidemiology Network contributed to development of the analysis plan, collection and analysis of primary data, data interpretation, and critically reviewed the revised initial draft of the manuscript. All members of the Respiratory Virus Global Epidemiology Network contributed to data collection, data analysis, and critically reviewed the manuscript. All authors read and approved the last draft for finalization.

For a full list of members of Respiratory Virus Global Epidemiology Network see appendix p2.

Declaration of interests

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